The Gut Microbiota and its Relationship to Post-Traumatic Stress Disorder: A review of the science

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Abstract

Problem statement: There is a growing body of evidence that supports a connection between gastrointestinal disease and mental illness, as well as the bi-directional effect of the gut-brain axis. Recent research supports the theory that bacteria in the gut also affects this gut brain axis and can impact mental health, particularly focusing on depression and anxiety. However, the discussion on the relationship between the gut microbiota and Post-traumatic stress disorder (PTSD) is limited.
Aims: This review aims to inform psychiatric nurses of the established research on the effects of the gut microbiota on PTSD. Nurses will receive the most up-to-date practice recommendations for the integration of gut care to positively impact outcomes for patients with PTSD.
Summary of evidence: Bacteria in the gut produce neurotransmitters as found in the brain and in the antidepressants that psychiatric nurses use daily (Dinan, Stilling, Stanton & Cryan, 2019). Additionally, these same antidepressants have been shown to alter gut the microbiota (Lukic, Getselter, Ziv, Oron, Reuveni, Koren, & Elliot, 2019). This knowledge is contributing to practice changes that allow for the integration of GI care and mental health care.
Conclusions: As we move towards a more integrated model of care, it is critical that the psychiatric nurse understand not only the gastrointestinal system, but the gut-brain axis and how the ingestion of bacteria and development of bacteria in the gut affects PTSD.

Introduction

The gut-brain connection is a hot topic in research, but the majority of studies focus on the connection between the gut and depression and anxiety. Research on PTSD and the impact of the gut microbiota is limited. This poster will review the current research on the relationship between PTSD and the gut microbiota, as well as gut changes that could potentially have an impact on the development and treatment of PTSD.

PTSD and the Gut Microbiota

Most studies on PTSD and the gut microbiota have been performed using a rat model. However, one study specifically examined the microbiota in human patients with PTSD. Bajaj, et. al. collected stool from 93 Veterans with cirrhosis of the liver and compared those with and without PTSD. They found that microbial diversity was lower in those with PTSD independent of antidepressant use (2019). The study may not be generalizable to all individuals with PTSD, as the study was performed only on male Veterans with combat-related PTSD. Another study compared 18 South Africans with PTSD to 12 individuals who had been exposed to a trauma but did not develop PTSD. Researchers identified a decreased total abundance of *Actinobacteria*, *Lentisphaerae*, and *Verrucomicrobia* in the group diagnosed with PTSD (Hemmings, et al., 2017).

PTSD in Rodent Models

The majority of studies reviewing the impact of the gut microbiota in PTSD use a rodent model of PTSD. Each study uses a form of prolonged and repeated stress to mimic the stress of PTSD in the rats or mice. In one such study, rats were exposed to an initial trauma of a physical injury, then repeated stress of chronic restraint. Rats who received the trauma only had a fairly stable microbiota, but those who experienced the chronic stress over 14 days showed a significant decrease in the bacteria *C. celatum*, with a predominance of the genera Corynebacterium and Bacteroides (Kelly, et al.,2021). This study identifies chronic stress as a potential contributor to alteration of microbial diversity after trauma, and the authors suggest that alteration may impact long-term outcomes.
Another such study followed a similar model, yet used adolescent rats. Differences in microbial diversity stabilized three weeks after the end of the chronic stress, yet the altered microbial metabolic profiles continued into adulthood (Xu, Wang, Krolick, Shi & Zhu, 2020)
Similarly, a small study of 16 rats mimicked the chronic stress of PTSD and found lower levels of serotonin in the brain, correlated with lower *Firmicutes, Bacteroidetes, Cyanobacteria, and Proteobacteria*, which were most relevant to the exhibited fear-like and anxiety-like behaviors and significan serotonin content reduction (Zhou, et al., 2020)..
Finally, a fourth study mimicked Gulf War conditions by exposing mice to chemicals that soldiers were exposed to in the Gulf War. Authors report that "chemical exposure caused significant dysbiosis in the gut that included increased abundance of phylum Firmicutes and Tenericutes, and decreased abundance of Bacteroidetes. Altered microbiome caused significant decrease in tight junction protein Occludin with a concomitant increase in Claudin-2, a signature of a leaky gut. Resultant leaching of gut caused portal endotoxemia that led to upregulation of toll like receptor 4 (TLR4) activation in the small intestine and the brain." They concluded that these chemical exposures were associated with neuroinflammation and GI distress, (Alhasson, et al., 2017).

Stress and the Gut Microbiota

PTSD is a form of chronic stress, as patients are often reliving the initial trauma in the form of flashbacks, nightmares, and intrusive memories. Therefore, it is critical to explore the effect of chronic stress on the gut microbiota as it relates to PTSD. One study showed that even a single 2-hour stressor affected the gut microbiota, and chronic exposure to stress significantly reduced the bacteria *Lactobacillus* in mice (Galley, et al., 2014). A similar study of stressed mice showed not only reduced *Lactobacillus*, but also increased circulating kynurenine levels. When researchers replaced the intestinal *Lactobacillus*, this intervention improved metabolic alterations and behavioral abnormalities, (Marin, et al., 2017).
Other studies have been able to induce GI symptoms by causing stress. One project experimented with both mice and humans. In the mice, they were able to induce symptoms of weight loss, bloody diarrhea, shortened colon length, and colonic inflammatory reaction thru the use of stress. In humans, the researchers administered questionnaires and found a correlation between perceived stress and Inflammatory Bowel Disease symptom severity, (Wang, et al., 2019).
Furthermore, one study showed that stress not only drastically alter the gut microbiota, but triggered the expansion of inflammation-promoting bacteria and a immune response, (Gao, et al., 2018).This is important because inflammation in the gut has been shown to weaken gut and blood-brain barriers. This loss of integrity leads to hyperpermeability and leaky gut. This leaky gut can then lead to further microbial imbalances in the gut, alteration of the gut-brain axis, and ultimately the production of neurotransmitters that affect mood and mental health symptomatology, (Doney, Cadoret, Dion-Albert, Lebel, & Menard, 2021).

The Microbiota and Neurotransmitters

The gut is home to many of the same neurotransmitters that are targeted in the psychotropic medications that nurses use to treat mental illnesses including PTSD. It is estimated that 95% of our serotonin is released into the gut by intestinal enterochromaffin cells (Berger, Gray, & Roth, 2009). " Lactobacillus and Bifidobacterium species produce gamma-aminobutyric acid (GABA); Escherichia, Bacillus and Saccharomyces spp. produce norepinephrine; Candida, Streptococcus, Escherichia and Enterococcus spp. produce 5HT; Bacillus produces dopamine; and Lactobacillus produces acetylcholine," (Dinan, Stilling, Stanton, & Cyran, 2015). This has lead researchers to investigate the effects of the antidepressants that target these same neurotransmitters as well as the potential treatment of mental illness with bacteria in the form of probiotics.

Antidepressants' Effect on the Microbiota

Recent studies reveal that antidepressants alter the gut microbiota. SSRIs have been shown to have antimicrobial effects, mainly against gram positive bacteria (Munoz-Bellido, Munoz-Criado, & Garcı´a-Rodrı´guez, 2000). In mice, the antidepressants fluoxetine, escitalopram, venlafaxine, duloxetine, and desipramine reduced richness and increased beta diversity of gut bacteria, reducing the abundance of Ruminococcus, Adlercreutzia, and an unclassified Alphaproteobacteria (Lukic, et al 2019). However, another study showed that fluoxetine and amitriptyline actually increased the abundance of other bacteria, particularly Bacteroides, Parabacteroides, Butyricimonas, Acetatifactor, and Tyzzerella, in rats(Zhang, Qu, Wang, & Yan, 2021).
In a further study, fluoxetine administered to mice reduced the bacteria Lactobacillus johnsonii and Bacteroidales S24-7 in the gut. Authors suggest that supplementation with bacteria may counteract some of the well-known gastrointestinal side effects of fluoxetine (Lyte, Daniels, & Schmitz-Esser, 2019).

Probiotic Interventions

Stress-related changes in the gut microbiota have lead researchers to begin to examine the use of probiotics as a treatment for mental health conditions, including PTSD. In a double-blind, placebo controlled study of 75 healthy volunteers, a probiotic supplement improved the stress-related GI symptoms of abdominal pain, nausea/vomiting, flatulence, and gas production compared to the control group (Diop, Guillou, & Durand, 2008).
One pilot study has assessed the use of a probiotic in the treatment of PTSD in Veterans. However, the sample size was small, with only 31 participants, and the results were inconclusive. Authors state that the supplement "resulted in a decrease in plasma C-reactive protein concentrations relative to the placebo group that approached statistical significance," (Brenner, et al., 2020).
Furthermore, probiotic supplementation has shown to increase levels of GABA in the brain (Bravo, et al., 2011; Janik, et al., 2016). An anxiolytic neurotransmitter, GABA has been shown to be reduced in Veterans exposed to trauma (Sheth, et al., 2019), and may be a target for treatment to calm some of the symptoms of PTSD.
A prebiotic supplement has shown promising results, exhibiting both antidepressant and anxiolytic effects in mice, as well as reducing stress-induced corticosterone release. With chronic use, researchers saw that the prebiotic began to normalize the effects of chronic stress on the gut microbiota (Burokas, et al., 2017).

Discussion

It is well established that corticotropin-releasing hormone (CRF), the stress hormone, has a negative effect on the gut by increasing inflammation and gut permeability and dysregulating gut motility. These changes may result in an environment that is not suitable for the survival of certain beneficial bacteria, particularly Lactobacillus (He, Guo, Zheng, & Yao, 2018). Furthermore, alterations of bacteria in the gut can contribute to neuroinflammation, impacting the production of serotonin, catecholamine, and glutamate, thereby altering brain function, (Lindquist, Hammamieh, & Pramod, 2020). Antidepressants that psychiatric nurses prescribe on a daily basis can contribute to the alteration of the gut microbiota.

Conclusions

Psychiatric nurses should be aware of the gut changes that take place with stress, inflammation, and the use of prescription antidepressants. The chronic stress of PTSD could contribute to GI symptomatology, while GI changes could alter neurotransmitter release and thereby affect symptoms of PTSD. Research into probiotics and prebiotics for the treatment of PTSD-related altered gut microbiota is limited, but promising.

References

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See handout for full references.